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                  substances identified in English-, French-, German-,
                  and Japanese-language basic patents from 2004-present
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 NEWS  4  NOV 26  CHEMSAFE now available on STN Easy
 NEWS  5  NOV 26  Two new SET commands increase convenience of STN
                  searching
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 NEWS  7  DEC 12  GBFULL now offers single source for full-text
                  coverage of complete UK patent families
 NEWS  8  DEC 17  Fifty-one pharmaceutical ingredients added to PS
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 NEWS 10  JAN 07  WPIDS, WPINDEX, and WPIX enhanced Japanese Patent
                  Classification Data

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              AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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=> s DOCK2
L1 207 DOCK2

=> s ELMO
L2 883 ELMO

=> s L1 and L2
L3 9 L1 AND L2

=> d L3 full 1-9
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L3 ANSWER 1 OF 9 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
AN 2008599701 EMBASE
TI Parallel phosphatidylinositol 3-kinase (PI3K)-dependent and Src-dependent pathways lead to CXCL8-mediated Rac2 activation and chemotaxis.
AU Richmond, Ann (correspondence)
CS Department of Veterans Affairs, School of Medicine, Vanderbilt University, Nashville, TN 37232, United States. ann.richmond@vanderbilt.edu
AU Sai, Jiqing; Raman, Dayanidhi; Richmond, Ann (correspondence)
CS Dept. of Cancer Biology, School of Medicine, Vanderbilt University, Nashville, TN 37232, United States. ann.richmond@vanderbilt.edu
AU Liu, Yuxin; Wikswo, John
CS VIIBRE and Biomedical Engineering, School of Engineering, Vanderbilt University, Nashville, TN 37212, United States.
SO Journal of Biological Chemistry, (26 Sep 2008) Vol. 283, No. 39, pp. 26538-26547.
Refs: 47
ISSN: 0021-9258 E-ISSN: 1083-351X CODEN: JBCHA3
PB American Society for Biochemistry and Molecular Biology Inc., 9650 Rockville Pike, Bethesda, MD 20814, United States.
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry

LA English
SL English
ED Entered STN: 16 Jan 2009
Last Updated on STN: 16 Jan 2009
AB The requirement for phosphatidylinositol 3-kinase (PI3K) in the establishment of cell polarity and motility in a number of cell types has recently come into question. In this study, we demonstrate that inhibition of PI3K by wortmannin in neutrophil-like differentiated HL60 cells expressing CXCR2 resulted in reduced cell motility but normal chemotaxis in response to a gradient of CXCL8. However, wortmannin inhibition of PI3K did impair the ability of cells to re-orient their polarity and respond quickly to a change in the direction of the CXCL8 gradient. We hypothesized that Src-regulated ELMO-Dock2 -Rac2 activation mediates chemotaxis in the absence of PI3K activity. Inhibition of Src with the small molecule inhibitor, PP2, or inhibition of Dock2 by shRNA knockdown confirmed the functional role of Src and Dock2 in regulating chemotaxis when PI3K was inhibited. Moreover, neutrophils isolated from bone marrow of hck(-/-)fgr(-/-)lyn(-/-) mice exhibited much more severe inhibition of chemotaxis when PI3K was blocked with wortmannin as compared with neutrophils isolated from bone marrow of wild-type mice. Thus, PI3K and Src-ELMO-Dock2 pathways work in parallel to activate Rac2 and modulate chemotaxis in response to a CXCL8 gradient in neutrophils.
CT Medical Descriptors:
animal cell
article
bone marrow
cell motility
cell polarity
cell strain HL 60
controlled study
enzyme activity
mouse
neutrophil
nonhuman
priority journal
CT Drug Descriptors:
4 amino 7 tert butyl 5 (4 chlorophenyl)pyrazolo[3,4 d]pyrimidine
guanine nucleotide binding protein
*interleukin 8
*phosphatidylinositol 3 kinase inhibitor
protein dock2
protein tyrosine kinase
*Rac2 protein
short hairpin RNA
unclassified drug
wortmannin
RN (interleukin 8) 114308-91-7; (protein tyrosine kinase) 80449-02-1; (wortmannin) 19545-26-7

L3 ANSWER 2 OF 9 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
AN 2002328924 EMBASE
TI The CDM protein DOCK2 in lymphocyte migration.
AU Reif, Karin (correspondence); Cyster, Jason G
CS Howard Hughes Medical Institute, Dept of Microbiology and Immunology, University of California San Francisco, San Francisco, CA 94143-0414, United States. kreif@itsa.ucsf.edu; cyster@itsa.ucsf.edu
AU Reif, Karin (correspondence)
CS Howard Hughes Medical Institute, Dept. of Microbiology, Univ. of California San Francisco, San Francisco, CA 94143-0414, United States. kreif@itsa.ucsf.edu

SO Trends in Cell Biology, (1 Aug 2002) Vol. 12, No. 8, pp. 368-373.
Refs: 58
ISSN: 0962-8924 CODEN: TCBIEK
PUI S 0962-8924(02)02330-9
CY United Kingdom
DT Journal; General Review; (Review)
FS 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 26 Sep 2002
Last Updated on STN: 26 Sep 2002
AB T and B lymphocytes migrate hundreds of micrometers each day to survey the body's lymphoid tissues for antigens. No other mammalian cell type undergoes such extensive and continual movement, raising the question of whether lymphocytes have specializations to support their migratory behavior. This possibility has recently gained support from studies of mice deficient in DOCK2, a member of the Caenorhabditis elegans Ced-5, mammalian DOCK180 and Drosophila melanogaster myoblast city (CDM) family of scaffolding proteins. Migration of lymphocytes, but not other cell types, is severely disrupted in DOCK2-deficient mice. Despite the conserved role of CDM molecules in regulating Rac activation and actin assembly, relatively little is known about how these molecules function. Here, we review the role of DOCK2 in lymphocyte homing to lymphoid tissues and discuss recent findings for other CDM family molecules that provide a basis for understanding how DOCK2 might function in lymphocytes.
CT Medical Descriptors:
B lymphocyte
Caenorhabditis elegans
cell type
chemotaxis
Drosophila melanogaster
*lymphocyte migration
lymphoid tissue
molecule
myoblast
nonhuman
nucleotide sequence
priority journal
protein assembly
protein expression
protein function
protein protein interaction
review
sequence homology
T lymphocyte
CT Drug Descriptors:
actin
chemokine
chemokine cxcl13
chemokine receptor CCR2
macrophage inflammatory protein 3beta
monocyte chemotactic protein 1
pertussis toxin
*protein
protein ced 10
protein Ced 12
protein Ced 5
protein DOCK180
protein DOCK2
protein ELMO 1

protein ELMO 2
protein ELMO 3
protein myoblast city
Rac protein
secondary lymphoid tissue chemokine
stromal cell derived factor 1
unclassified drug

RN (macrophage inflammatory protein 3beta) 181030-14-8; (pertussis toxin) 70323-44-3; (protein) 67254-75-5

GEN GENBANK AB002297 referred number; GENBANK AC003077 referred number; GENBANK AC003080 referred number; GENBANK AF010409 referred number; GENBANK D50857 referred number; GENBANK D86964 referred number; GENBANK NM_014705 referred number; GENBANK U20939 referred number

L3 ANSWER 3 OF 9 MEDLINE on STN

AN 2008614691 MEDLINE
DN PubMed ID: 18662984

TI Parallel phosphatidylinositol 3-kinase (PI3K)-dependent and Src-dependent pathways lead to CXCL8-mediated Rac2 activation and chemotaxis.

AU Sai Jiqing; Raman Dayanidhi; Liu Yuxin; Wikswo John; Richmond Ann
CS Department of Cancer Biology, School of Medicine, Vanderbilt University, Nashville, Tennessee 37232, USA.

NC CA34590 (United States NCI)
CA68485 (United States NCI)
U54CA113007 (United States NCI)
SO The Journal of biological chemistry, (2008 Sep 26) Vol. 283, No. 39, pp. 26538-47. Electronic Publication: 2008-07-28.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LA English
FS Priority Journals
EM 200811
ED Entered STN: 23 Sep 2008
Last Updated on STN: 11 Nov 2008
Entered Medline: 10 Nov 2008

AB The requirement for phosphatidylinositol 3-kinase (PI3K) in the establishment of cell polarity and motility in a number of cell types has recently come into question. In this study, we demonstrate that inhibition of PI3K by wortmannin in neutrophil-like differentiated HL60 cells expressing CXCR2 resulted in reduced cell motility but normal chemotaxis in response to a gradient of CXCL8. However, wortmannin inhibition of PI3K did impair the ability of cells to re-orient their polarity and respond quickly to a change in the direction of the CXCL8 gradient. We hypothesized that Src-regulated ELMO-Dock2 -Rac2 activation mediates chemotaxis in the absence of PI3K activity. Inhibition of Src with the small molecule inhibitor, PP2, or inhibition of Dock2 by shRNA knockdown confirmed the functional role of Src and Dock2 in regulating chemotaxis when PI3K was inhibited. Moreover, neutrophils isolated from bone marrow of hck(-/-)fgr(-/-)lyn(-/-) mice exhibited much more severe inhibition of chemotaxis when PI3K was blocked with wortmannin as compared with neutrophils isolated from bone marrow of wild-type mice. Thus, PI3K and Src-ELMO-Dock2 pathways work in parallel to activate Rac2 and modulate chemotaxis in response to a CXCL8 gradient in neutrophils.

CT 1-Phosphatidylinositol 3-Kinase
Androstadienes: PD, pharmacology
Animals
Cell Polarity: PH, physiology

Chemotaxis: DE, drug effects
*Chemotaxis: PH, physiology
Guanine Nucleotide Exchange Factors: GE, genetics
Guanine Nucleotide Exchange Factors: ME, metabolism
HL-60 Cells
Humans
Interleukin-8: GE, genetics
*Interleukin-8: ME, metabolism
Mice
Mice, Knockout
Nerve Tissue Proteins: GE, genetics
Nerve Tissue Proteins: ME, metabolism
Neutrophils: CY, cytology
*Neutrophils: ME, metabolism
Protein Kinase Inhibitors: PD, pharmacology
Proto-Oncogene Proteins c-hck: GE, genetics
Proto-Oncogene Proteins c-hck: ME, metabolism
Pyrimidines: PD, pharmacology
Receptors, Interleukin-8B: GE, genetics
*Receptors, Interleukin-8B: ME, metabolism
Signal Transduction: DE, drug effects
Signal Transduction: PH, physiology
rac GTP-Binding Proteins: GE, genetics
*rac GTP-Binding Proteins: ME, metabolism
src-Family Kinases: GE, genetics
*src-Family Kinases: ME, metabolism
RN 19545-26-7 (wortmannin)
CN 0 (AG 1879); 0 (Androstadienes); 0 (DOCK2 protein, human); 0 (DOCK3 protein, human); 0 (FGD1-related Cdc42-GEF protein, human); 0 (Guanine Nucleotide Exchange Factors); 0 (IL8 protein, human); 0 (Interleukin-8); 0 (Nerve Tissue Proteins); 0 (Protein Kinase Inhibitors); 0 (Pyrimidines); 0 (Receptors, Interleukin-8B); EC 2.7.1.112 (HCK protein, human); EC 2.7.1.112 (Hck protein, mouse); EC 2.7.1.112 (Proto-Oncogene Proteins c-hck); EC 2.7.1.112 (lyn protein-tyrosine kinase); EC 2.7.1.112 (src-Family Kinases); EC 2.7.1.137 (1-Phosphatidylinositol 3-Kinase); EC 3.6.1.- (rac2 GTP-binding protein); EC 3.6.5.2 (rac GTP-Binding Proteins)

L3 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2008:1130400 CAPLUS
DN 149:353567
ED Entered STN: 19 Sep 2008
TI Parallel Phosphatidylinositol 3-Kinase (PI3K)-dependent and Src-dependent Pathways Lead to CXCL8-mediated Rac2 Activation and Chemotaxis
AU Sai, Jiqing; Raman, Dayanidhi; Liu, Yuxin; Wikswo, John; Richmond, Ann
CS Department of Cancer Biology, School of Medicine, Vanderbilt University, Nashville, TN, 37232, USA
SO Journal of Biological Chemistry (2008), 283(39), 26538-26547
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 15-5 (Immunochemistry)
AB The requirement for phosphatidylinositol 3-kinase (PI3K) in the establishment of cell polarity and motility in a number of cell types has recently come into question. In this study, the authors demonstrate that inhibition of PI3K by wortmannin in neutrophil-like differentiated HL60 cells expressing CXCR2 resulted in reduced cell motility but normal chemotaxis in response to a gradient of CXCL8. However, wortmannin inhibition of PI3K did impair the ability of cells to re-orient their polarity and respond quickly to a change in the direction of the CXCL8 gradient. The authors hypothesized that Src-regulated ELMO-Dock2-Rac2 activation mediates chemotaxis in the absence of PI3K

activity. Inhibition of Src with the small mol. inhibitor, PP2, or inhibition of Dock2 by shRNA knockdown confirmed the functional role of Src and Dock2 in regulating chemotaxis when PI3K was inhibited. Moreover, neutrophils isolated from bone marrow of hck-/-fgr-/-lyn-/- mice exhibited much more severe inhibition of chemotaxis when PI3K was blocked with wortmannin as compared with neutrophils isolated from bone marrow of wild-type mice. Thus, PI3K and Src-ELMO-Dock2 pathways work in parallel to activate Rac2 and modulate chemotaxis in response to a CXCL8 gradient in neutrophils.

ST phosphatidylinositol kinase CXCL8 chemokine signaling neutrophil chemotaxis

IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD182; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT CXC chemokine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CXCR2; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Dock2; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ELMO1; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT G proteins (guanine nucleotide-binding proteins)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Rac2; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Neutrophil
(chemotaxis; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Chemotaxis
(neutrophil; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Cell polarity
Human
Signal transduction
(phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Interleukin 8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT Interleukin 8 receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β; phosphatidylinositol kinase- and Src-dependent signaling pathways for interleukin 8-induced Rac2 activation in neutrophil chemotaxis)

IT 115926-52-8, Phosphatidylinositol 3-kinase 141349-89-5, Src kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phosphatidylinositol kinase- and Src-dependent signaling pathways for

interleukin 8-induced Rac2 activation in neutrophil chemotaxis)
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L3 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2004:471072 CAPLUS
DN 141:17607
ED Entered STN: 10 Jun 2004
TI Functional domain and associated molecule of DOCK2 essentially required in lymphocyte migration
IN Fukui, Yoshinori; Sasazuki, Takehiko
PA Japan Science and Technology Agency, Japan
SO PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DT Patent

LA Japanese
IC ICM G01N033-566
ICS G01N033-50; G01N033-15; C12N015-12
CC 1-7 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004048974	A1	20040610	WO 2003-JP14538	20031114
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	JP 3568522	B2	20040922		
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	EP 1580556	A1	20050928	EP 2003-772787	20031114
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	WO 2003-JP14538	W	20031114		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004048974	ICM	G01N033-566
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	ECLA	G01N033/564; S01N
JP 2004177226	IPCI	G01N0033-50 [ICM,7]; A61K0045-00 [ICS,7]; A61P0037-02 [ICS,7]; A61P0037-06 [ICS,7]; A61P0037-08 [ICS,7]; A61P0037-00 [ICS,7,C*]; A61P0043-00 [ICS,7]; G01N0033-15 [ICS,7]; G01N0033-566 [ICS,7]; C12N0015-09 [ICS,7]
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		[I,C*]; A61P0037-02 [I,A]; A61P0037-06 [I,A]; A61P0037-08 [I,A]; A61P0043-00 [I,C*]; A61P0043-00 [I,A]; C12N0015-09 [I,C*]; C12N0015-09 [I,A]; C12N0015-12 [I,C*]; C12N0015-12 [I,A]; G01N0033-15 [I,C*]; G01N0033-15 [I,A]; G01N0033-50 [I,C*]; G01N0033-50 [I,A]; G01N0033-564 [I,C*]; G01N0033-564 [I,A]; G01N0033-566 [I,C*]; G01N0033-566 [I,A]
	ECLA	G01N033/564
EP 1580556	IPCI	G01N0033-566 [I,C]; G01N0033-566 [I,A]
	IPCR	A61K0045-00 [I,C*]; A61K0045-00 [I,A]; A61P0037-00 [I,C*]; A61P0037-02 [I,A]; A61P0037-06 [I,A]; A61P0037-08 [I,A]; A61P0043-00 [I,C*]; A61P0043-00 [I,A]; C12N0015-09 [I,C*]; C12N0015-09 [I,A]; C12N0015-12 [I,C*]; C12N0015-12 [I,A]; G01N0033-15 [I,C*]; G01N0033-15 [I,A]; G01N0033-50 [I,C*]; G01N0033-50 [I,A]; G01N0033-564 [I,C*]; G01N0033-564 [I,A]
	ECLA	G01N033/564; S01N
JP 2004226418	IPCI	G01N0033-50 [I,A]; G01N0033-15 [I,A]; G01N0033-53 [I,A]; G01N0033-566 [I,A]; C07K0014-47 [N,A]; C07K0014-435 [N,C*]
	IPCR	C07K0014-435 [N,C*]; C07K0014-47 [N,A]; G01N0033-15 [I,A]; G01N0033-15 [I,C*]; G01N0033-50 [I,A]; G01N0033-50 [I,C*]; G01N0033-53 [I,A]; G01N0033-53 [I,C*]; G01N0033-566 [I,A]; G01N0033-566 [I,C*]
	FTERM	2G045/AA34; 2G045/AA35; 2G045/AA40; 2G045/BA11; 2G045/BB50; 2G045/DA13; 2G045/DA36; 2G045/FB02; 4H045/AA30; 4H045/BA10; 4H045/CA40; 4H045/EA50; 4H045/FA74
US 20060234294	IPCI	G01N0033-53 [I,A]
	NCL	435/007.100
	ECLA	G01N033/564

AB It is intended to provide a method of screening a substance interfering the association of DOCK2 with ELMO1, a method of screening a substance interfering the association of ELMO1 with Tiam1, a method of searching for remedies for immune-related diseases such as allergy, autoimmune diseases, GvH and graft rejection by using these screening methods, etc. It is found out that a DOCK2 mutant lacking 504 amino acid residues at the N-end of DOCK2 shows a remarkably lowered ability to activate Rac and cannot induce actin polymerization ELMO1 is identified as a mol. binding to this region. It is also found out that DOCK2 is associated with ELMO1 via the SH3 domain. It is furthermore found out that ELMO1 binds to Tiam1 which acts as a Rac-specific GDP/GTP exchange factor (GEF). Thus, it is found out that DOCK 2 recruits Tiam1 via ELMO1 and thus activates Rac.

ST DOCK2 ELMO1 lymphocyte migration immunosuppressant screening

IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(DOCK 2; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)

IT G proteins (guanine nucleotide-binding proteins)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Rac; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)

IT Allergy inhibitors
Autoimmune disease
Drug screening
Human
Immunosuppressants
Molecular cloning

Mus
(functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
IT Transplant and Transplantation
(graft-vs.-host reaction; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
IT Cell migration
(lymphocyte; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
IT Lymphocyte
(migration; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
IT 700389-44-2, Protein DOCK 2 (mouse) 700389-45-3, Protein DOCK 2 (human) 700389-46-4, Protein ELMO 1 (mouse) 700389-47-5, Protein ELMO 1 (human)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
IT 700390-52-9 700390-53-0
RL: PRP (Properties)
(unclaimed protein sequence; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
IT 92000-76-5
RL: PRP (Properties)
(unclaimed sequence; functional domain and associated mol. of DOCK2 essentially required in lymphocyte migration)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 2002, V296, P716
(2) Anon; BIOCHIMICA ET BIOPHYSICA ACTA 1999, V1452, P179
(3) Anon; CELL 2001, V107, P27
(4) Anon; NATURE 1995, V375, P338
(5) Anon; NATURE 2001, V412, P826

L3 ANSWER 6 OF 9 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2008:598610 BIOSIS
DN PREV200800598609
TI Parallel phosphatidylinositol 3-kinase (PI3K)-dependent and Src-dependent pathways lead to CXCL8-mediated Rac2 activation and chemotaxis.
AU Sai, Jiqing; Raman, Dayanidhi; Liu, Yuxin; Wikswo, John; Richmond, Ann [Reprint Author]
CS Vanderbilt Univ, Sch Med, Dept Canc Biol, 221 Kirkland Hall, Nashville, TN 37232 USA
ann.richmond@vanderbilt.edu
SO Journal of Biological Chemistry, (SEP 26 2008) Vol. 283, No. 39, pp. 26538-26547.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 29 Oct 2008
Last Updated on STN: 29 Oct 2008
AB The requirement for phosphatidylinositol 3-kinase (PI3K) in the establishment of cell polarity and motility in a number of cell types has recently come into question. In this study, we demonstrate that inhibition of PI3K by wortmannin in neutrophil-like differentiated HL60 cells expressing CXCR2 resulted in reduced cell motility but normal chemotaxis in response to a gradient of CXCL8. However, wortmannin inhibition of PI3K did impair the ability of cells to re-orient their polarity and respond quickly to a change in the direction of the CXCL8 gradient. We hypothesized that Src-regulated ELMO-Dock2 -Rac2 activation mediates chemotaxis in the absence of PI3K activity.

Inhibition of Src with the small molecule inhibitor, PP2, or inhibition of Dock2 by shRNA knockdown confirmed the functional role of Src and Dock2 in regulating chemotaxis when PI3K was inhibited. Moreover, neutrophils isolated from bone marrow of hck(-/-) fgr(-/-) lyn(-/-) mice exhibited much more severe inhibition of chemotaxis when PI3K was blocked with wortmannin as compared with neutrophils isolated from bone marrow of wild-type mice. Thus, PI3K and Src-ELMO-Dock2 pathways work in parallel to activate Rac2 and modulate chemotaxis in response to a CXCL8 gradient in neutrophils.

CC Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Animal 03506
Genetics - Human 03508
Biochemistry studies - Carbohydrates 10068
Enzymes - General and comparative studies: coenzymes 10802
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Immunology - General and methods 34502

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics)

IT Parts, Structures, & Systems of Organisms
neutrophil: immune system, blood and lymphatics; bone marrow: immune system, blood and lymphatics

IT Chemicals & Biochemicals
CXCL8; wortmannin; phosphatidylinositol 3-kinase [PI3K] [EC 2.7.1.137]; Rac2

IT Miscellaneous Descriptors
cell motility; chemotaxis; cell polarity; Src-dependent pathway

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HL60 cell line (cell_line): human leukemia cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 19545-26-7 (wortmannin)
115926-52-8 (phosphatidylinositol 3-kinase)
115926-52-8 (PI3K)
115926-52-8 (EC 2.7.1.137)

GEN mouse shRNA gene (Muridae): expression

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AN 2008:1148195 SCISEARCH

GA The Genuine Article (R) Number: 350GV

TI Parallel phosphatidylinositol 3-kinase (PI3K)-dependent and Src-dependent pathways lead to CXCL8-mediated Rac2 activation and chemotaxis

AU Richmond, Ann (Reprint)

CS Vanderbilt Univ, Sch Med, Dept Canc Biol, 221 Kirkland Hall, Nashville, TN 37232 USA (Reprint)
E-mail: ann.richmond@vanderbilt.edu

AU Sai, Jiqing; Raman, Dayanidhi; Richmond, Ann (Reprint)
CS Vanderbilt Univ, Sch Med, Dept Canc Biol, Nashville, TN 37232 USA
    E-mail: ann.richmond@vanderbilt.edu
AU Richmond, Ann (Reprint)
CS Vanderbilt Univ, Sch Med, Dept Vet Affairs, Nashville, TN 37232 USA
    E-mail: ann.richmond@vanderbilt.edu
AU Liu, Yuxin; Wikswo, John
CS Vanderbilt Univ, Sch Engn, VIIBRE & Biomed Engn, Nashville, TN 37212 USA
CYA USA
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (26 SEP 2008) Vol. 283, No. 39, pp. 26538-26547.
    ISSN: 0021-9258.
PB AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
DT Article; Journal
LA English
REC Reference Count: 47
ED Entered STN: 2 Oct 2008
    Last Updated on STN: 23 Oct 2008
AB The requirement for phosphatidylinositol 3-kinase (PI3K) in the establishment of cell polarity and motility in a number of cell types has recently come into question. In this study, we demonstrate that inhibition of PI3K by wortmannin in neutrophil-like differentiated HL60 cells expressing CXCR2 resulted in reduced cell motility but normal chemotaxis in response to a gradient of CXCL8. However, wortmannin inhibition of PI3K did impair the ability of cells to re-orient their polarity and respond quickly to a change in the direction of the CXCL8 gradient. We hypothesized that Src-regulated ELMO-Dock2 -Rac2 activation mediates chemotaxis in the absence of PI3K activity. Inhibition of Src with the small molecule inhibitor, PP2, or inhibition of Dock2 by shRNA knockdown confirmed the functional role of Src and Dock2 in regulating chemotaxis when PI3K was inhibited. Moreover, neutrophils isolated from bone marrow of hck(-/-) fgr(-/-) lyn(-/-) mice exhibited much more severe inhibition of chemotaxis when PI3K was blocked with wortmannin as compared with neutrophils isolated from bone marrow of wild-type mice. Thus, PI3K and Src-ELMO-Dock2 pathways work in parallel to activate Rac2 and modulate chemotaxis in response to a CXCL8 gradient in neutrophils.
CC BIOCHEMISTRY & MOLECULAR BIOLOGY
STP KeyWords Plus (R): NUCLEOTIDE EXCHANGE ACTIVITY; NEUTROPHIL CHEMOTAXIS; FAMILY; PI3K-GAMMA; PROTEINS; POLARITY; DOCK180; CELLS; DICTYOSTELIUM; ELMO1
RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	ARN PG (RPG)	Referenced Work (RWK)
ANDREW N	2007	9	193	NAT CELL BIOL
BENARD V	1999	274	13198	J BIOL CHEM
BOXIO R	2004	75	604	J LEUKOCYTE BIOL
CAMPS M	2005	11	936	NAT MED
CHEN L F	2007	12	603	DEV CELL
COTE J F	2005	7	797	NAT CELL BIOL
COTE J F	2006	406	41	METHOD ENZYMOL
COTE J F	2002	115	4901	J CELL SCI
DEBAKKER C D	2004	14	2208	CURR BIOL
FERGUS G J	2007	9	86	NAT CELL BIOL
FILIPPI M D	2004	5	744	NAT IMMUNOL
GRIMSLEY C M	2004	279	6087	J BIOL CHEM
GU Y	2001	276	15929	J BIOL CHEM
GUMIENNY T L	2001	107	27	CELL
HASEGAWA H	1996	16	1770	MOL CELL BIOL
HEIT B	2008	9	743	NAT IMMUNOL

HEIT B	2008	121	205	J CELL SCI
HIRSCH E	2000	287	1049	SCIENCE
HOELLER O	2007	17	813	CURR BIOL
KATOH H	2003	424	461	NATURE
KUNISAKI Y	2006	174	647	J CELL BIOL
LI S J	2002	169	5043	J IMMUNOL
LI Z	2000	287	1046	SCIENCE
LIU Y X	2008	10	499	BIOMED MICRODEVICES
LOOVERS H M	2006	17	1503	MOL BIOL CELL
LOWELL C A	1994	8	387	GENE DEV
LU M J	2006	406	388	METHOD ENZYMOL
LU M J	2005	15	371	CURR BIOL
MA Y C	2000	102	635	CELL
MELLER N	2005	118	4937	J CELL SCI
NEEL N F	2007	120	1559	J CELL SCI
NISHIHARA H	2002	100	3968	BLOOD
NOMBELAARRIETA C	2004	21	429	IMMUNITY
PARENTE C A	1998	95	81	CELL
ROBERTS A W	1999	10	183	IMMUNITY
SAI J Q	2006	281	35931	J BIOL CHEM
SANUI T	2003	102	2948	BLOOD
SASAKI T	2000	287	1040	SCIENCE
SERVANT G	2000	287	1037	SCIENCE
SHINOHARA M	2002	416	759	NATURE
SMITH L D	2007	19	2528	CELL SIGNAL
TAKEDA K	2007	282	11874	J BIOL CHEM
VANHAASTERT P J M	2007	177	809	J CELL BIOL
WANG F	2002	4	513	NAT CELL BIOL
WEINER O D	2002	4	509	NAT CELL BIOL
WELCH H C E	2002	108	809	CELL
YOKOYAMA N	2005	44	8841	BIOCHEMISTRY-US

L3 ANSWER 8 OF 9 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2006:285078 SCISEARCH
GA The Genuine Article (R) Number: BDV97
TI Dock180-ELMO cooperation in Rac activation
AU Lu M J (Reprint)
CS Univ Virginia, Carter Immunol Ctr, Charlottesville, VA 22903 USA (Reprint)
AU Ravichandran K S
CYA USA
SO METHODS IN ENZYMOLOGY, VOL 406, REGULATORS AND EFFECTORS OF SMALL GTPASES: RHO FAMILY, (2006) Vol. 406, pp. 388-402.
ISSN: 0076-6879.
PB ELSEVIER ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA 92101-4495 USA.
DT General Review; Journal
LA English
REC Reference Count: 29
ED Entered STN: 24 Mar 2006
Last Updated on STN: 10 Aug 2006
AB Dock180 superfamily of proteins has been recently identified as novel, unconventional guanine nucleotide exchange factors (GEF) for Rho-family GTPases. Unlike most other GEFs for Rho-family GTPases, Dock180 family members do not contain the characteristic Dbl homology (DH) domain. Instead, they use a conserved "Docker" or "CZH2" domain to mediate the nucleotide exchange on Rho-family GTPases. The Dock180 family members are evolutionarily conserved from worms to mammals. They play critical roles in a number of biological processes essential for the normal development of entire organisms, as well as for the physiological responses of these organisms, including removal of apoptotic cells and directed cell migration in C. elegans; myoblast fusion, and dorsal closure in

Drosophila; lymphocyte migration, T-cell activation, tumor metastasis, HIV infection, and development of neuronal degenerative diseases in mammals. All these biological activities of the Dock180 family members have been linked to their ability to activate their specific GTPase substrate. At least four members of the Dock180 family bind to another evolutionarily conserved protein ELMO to optimally activate the Rac GTPase. The best characterized is the Rac activation by the Dock180-ELMO complex. ELMO modulates the Rac activation by Dock180 by means of at least three distinct mechanisms: helping Dock180 stabilize Rac in its nucleotide-free transition state; relieving a self-inhibition of Dock180; and targeting Dock180 to the plasma membrane to gain access to Rac. Thus, Dock180 and ELMO function together as a bipartite GEF to optimally activate Rac on upstream stimulation to mediate the engulfment of apoptotic cells and cell migration.

CC BIOCHEMICAL RESEARCH METHODS; BIOCHEMISTRY & MOLECULAR BIOLOGY

STP KeyWords Plus (R): NUCLEOTIDE-EXCHANGE FACTORS; CELL-MIGRATION; RHO-GTPASES; CRKII/DOCK180/RAC PATHWAY; APOPTOTIC CELLS; PH DOMAIN; PROTEIN; PHAGOCYTOSIS; ELEGANS; DOCK2

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	ARN PG (RPG)	Referenced Work (RWK)
ALBERT M L	2000	2	899	NAT CELL BIOL
BISHOP A L	2000	348	241	BIOCHEM J 2
BRUGNERA E	2002	4	574	NAT CELL BIOL
COTE J F	2002	115	4901	J CELL SCI
DEBAKKER C D	2004	14	2208	CURR BIOL
ERICKSON M R S	1997	138	589	J CELL BIOL
FUKUI Y	2001	412	826	NATURE
GRIMSLEY C M	2004	279	6087	J BIOL CHEM
GUMIENNY T L	2001	107	27	CELL
HASEGAWA H	1996	16	1770	MOL CELL BIOL
HOFFMAN G R	2002	513	85	FEBS LETT
ISHIMARU S	2004	23	3984	EMBO J
KATOH H	2003	424	461	NATURE
KIYOKAWA E	1998	12	3331	GENE DEV
LU M J	2004	11	756	NAT STRUCT MOL BIOL
LU M J	2005	15	371	CURR BIOL
MELLER N	2002	4	639	NAT CELL BIOL
NAMEKATA K	2004	279	14331	J BIOL CHEM
NISHIKIMI A	2005	579	1039	FEBS LETT
REDDIEN P W	2000	2	131	NAT CELL BIOL
ROSSMAN K L	2005	6	167	NAT REV MOL CELL BIO
ROSSMAN K L	2003	278	18393	J BIOL CHEM
SANUI T	2003	19	119	IMMUNITY
SANUI T	2003	102	2948	BLOOD
SCHMIDT A	2002	16	1587	GENE DEV
WU Y C	1998	392	501	NATURE
WU Y C	2001	1	491	DEV CELL
YAJNIK V	2003	112	673	CELL
ZHOU W S	2001	12	1	J VIS COMMUN IMAGE R

L3 ANSWER 9 OF 9 DISSABS COPYRIGHT (C) 2009 ProQuest Information and Learning Company; All Rights Reserved on STN

AN 2008:59054 DISSABS Order Number: AAI3304335

TI The dock family of atypical guanine nucleotide exchange factors: Regulation by ELMO1 and RhoG

AU Holley, Cynthia P. [Ph.D.]; Sondek, John [advisor]

CS The University of North Carolina at Chapel Hill (0153)

SO Dissertation Abstracts International, (2008) Vol. 69, No. 4B, p. 2167. Order No.: AAI3304335. 121 pages.
ISBN: 978-0-549-53518-8.

DT Dissertation
FS DAI
LA English
ED Entered STN: 20081024
Last Updated on STN: 20081024
AB The Dock family of proteins regulates diverse biological processes including cell migration, phagocytosis and neuronal polarization. These proteins contain a unique type of guanine nucleotide exchange factor (GEF) domain, and function as GEFs for Rho-family GTPases. Several Dock-family proteins form complexes with ELMO proteins and the Dock/ELMO complex acts as a bi-partite GEF for Rac. Molecular details of how the Dock/ELMO complexes bind and exchange nucleotide on Rac are critical for our understanding of their biological effects, yet remain poorly defined.

As described here, purified Dock2/ELMO1 complex is a stable heterotetramer composed of two molecules each of Dock2 and ELMO1. This heterotetramer coordinates a single molecule of nucleotide-free Rac. We identify an inhibitory conformation within ELMO1 mediated through contacts between the N- and C-terminal regions of ELMO1 and describe a mechanism for relief of this inhibition through the binding of RhoG, another Rho-family GTPase. The interaction between RhoG and ELMO1 is both nucleotide-dependent, and dependent upon the C-terminal polybasic region of RhoG. These data provide fundamentally important molecular insights into the composition of the Dock/ELMO complex and regulation of nucleotide exchange via the Dock/ELMO proteins.
CC 0786 BIOPHYSICS, GENERAL

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=>
=> S L3 and screening
0 DOCK2
6 SCREENING
L4 0 L3 AND SCREENING

=> S DOCK2 and ELMO and screening
0 DOCK2
6 SCREENING
L5 0 DOCK2 AND ELMO AND SCREENING

=> s Ced-12 and DOCK2
29 12
0 CED-12
(CED(W)12)
0 DOCK2
L6 0 CED-12 AND DOCK2

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=> d his full

     (FILE 'HOME' ENTERED AT 16:45:35 ON 29 JAN 2009)

     FILE 'EMBASE, MEDLINE, CAPLUS, BIOSIS, SCISEARCH, DISSABS, REGISTRY'
     ENTERED AT 16:48:12 ON 29 JAN 2009
L1           207 SEA ABB=ON  PLU=ON  DOCK2
L2           883 SEA ABB=ON  PLU=ON  ELMO
L3             9 SEA ABB=ON  PLU=ON  L1 AND L2
               D L3 FULL 1-9

     FILE 'STNGUIDE' ENTERED AT 16:49:59 ON 29 JAN 2009
L4             0 SEA ABB=ON  PLU=ON  L3 AND SCREENING
L5             0 SEA ABB=ON  PLU=ON  DOCK2 AND ELMO AND SCREENING
L6             0 SEA ABB=ON  PLU=ON  CED-12 AND DOCK2


     FILE HOME

     FILE EMBASE
      FILE COVERS 1974 TO 29 Jan 2009 (20090129/ED)

      EMBASE was reloaded on March 30, 2008.

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     FILE MEDLINE
      FILE LAST UPDATED: 28 Jan 2009 (20090128/UP).  FILE COVERS 1949 TO DATE.

      MEDLINE and LMEDLINE have been updated with the 2009 Medical Subject
      Headings (MeSH) vocabulary and tree numbers from the U.S.  National Libra
      of Medicine (NLM).  Additional information is available at

      http://www.nlm.nih.gov/pubs/techbull/nd08/nd08_medline_data_changes_2009.

      This file contains CAS Registry Numbers for easy and accurate
      substance identification.

      See HELP RANGE before carrying out any RANGE search.

      MEDLINE Accession Numbers (ANs) for records from 1950-1977 have
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      AN will retrieve the same record.  The 10-digit ANs can be expanded,
      searched, and displayed in all records from 1949 to the present.

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FILE COVERS 1907 - 29 Jan 2009 VOL 150 ISS 5
FILE LAST UPDATED: 28 Jan 2009 (20090128/ED)

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reclassification data for the third quarter of 2008.

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FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

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DICTIONARY FILE UPDATES: 28 JAN 2009 HIGHEST RN 1097265-75-2

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LAST RELOADED: Jan 23, 2009 (20090123/UP).

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CA SUBSCRIBER PRICE	0.00	-1.64

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